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List of Abbreviations

Abbreviation	Definition
CoV	coronavirus
COVID-19	coronavirus disease caused by the 2019 novel coronavirus
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ERD	enhanced respiratory disease
GLP	Good Laboratory Practices
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IM	intramuscular
LNP	lipid nanoparticle
mRNA	messenger RNA
NHP	nonhuman primate
OECD	Organisation for Economic Co-operation and Development
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol
S	spike
S-2P	SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain
SARS	severe acute respiratory syndrome
SARS-CoV-2	2019 novel coronavirus
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
WT	wild-type

2.6.1 INTRODUCTION

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome and severe acute respiratory syndrome (SARS). An outbreak of the CoV disease (COVID-19) caused by the 2019 novel CoV (2019-nCoV, later designated SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019, and has spread throughout China and across the 6 World Health Organization regions ([WHO 2020](#)). A CoV ribonucleic acid was quickly identified in some of these patients. There is currently no European Medicines Agency-approved vaccine against SARS-CoV-2. Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, but no proven therapy currently exists. Therefore, there is an urgent public health need for the rapid development of novel interventions, including vaccines, to prevent the spread of this disease.

ModernaTX, Inc. (Sponsor) has used its messenger RNA (mRNA)-based, rapid-response, proprietary vaccine platform to develop mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2. mRNA-1273 contains a single mRNA that encodes for the full-length SARS-CoV-2 spike (S) glycoprotein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilize the S protein into the prefusion conformation. The mRNA is combined in a mixture of 4 ionizable, structural, helper, and polyethylene glycol lipids common to the Sponsor's mRNA vaccine platform: heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (SM-102); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol (PEG2000-DMG). mRNA-1273 Injection (Drug Product) is provided as a sterile liquid for injection at a concentration of 0.20 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 4.3 mM sodium acetate at pH 7.5.

The clinical development of mRNA-1273 to support its use in the adult population consists of 3 ongoing clinical trials being conducted in the United States: a Phase 1, open-label, dose-ranging study sponsored by the Division of Microbiology and Infectious Diseases of the National Institute of Allergy and Infectious Diseases, a Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study conducted by the Sponsor, and a Phase 3, randomized, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of the vaccine conducted by the Sponsor. The development of mRNA-1273 has been accelerated to address the current COVID-19 outbreak, benefitting from the uniquely rapid and scalable manufacturing processes that have been developed for this vaccine.

2.6.1.1 Nonclinical Development Program for mRNA-1273

The nonclinical pharmacology, pharmacokinetics and tissue distribution, and toxicology studies conducted with mRNA-1273 and other mRNA-based vaccines formulated in SM-102-containing LNPs support the intended clinical use of mRNA-1273. The program was designed in accordance with guidelines applicable at the time the studies were conducted, including relevant International Conference on Harmonisation (ICH) and other global regulatory guidelines and Good Laboratory Practice (GLP) regulations. The pivotal nonclinical safety studies were conducted according to the Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (ENV/MC/CHEM[98]17) or GLP regulations in other countries that are signatories to the OECD Mutual Acceptance of Data agreement (eg, US Food and Drug Administration Code of Federal Regulations Title 21, Part 58; Good Laboratory Practice for Nonclinical Laboratory Studies).

The nonclinical studies were conducted in mice, rats, hamsters, and rhesus macaques, which are species determined to be relevant for the assessment of the immunogenicity, efficacy, and safety of mRNA-1273.

2.6.1.1.1 Nonclinical Pharmacology Program

Nonclinical pharmacology evaluations were conducted in young and aged wild-type (WT) mouse (BALB/c, C57/BL6, and B6C3F1 strains), Syrian golden hamster, and rhesus macaque (nonhuman primate [NHP]) animal models to characterize the immunogenicity of mRNA-1273 as well as its effects on viral replication and disease progression and to assess theoretical concerns of vaccine-associated enhanced respiratory disease (ERD) after viral challenge, which has been previously observed with some vaccines against other viral respiratory diseases. Additionally, the immunogenicity of mRNA-1273 was assessed as part of a non-GLP repeat-dose toxicology study in Sprague Dawley rats.

Immunogenicity was characterized in young and aged mice, rats, hamsters, and NHPs through the evaluation of the humoral (immunoglobulin [Ig] G binding antibodies), cellular (T-cell cytokines), and/or functional (neutralizing antibodies) immune responses elicited by prime-only and prime/boost immunization schedules with a range of mRNA-1273 doses.

Protection by mRNA-1273 immunization was assessed in young and aged mice, hamsters, and NHPs immunized on prime-only and prime/boost schedules followed by viral challenge with high doses of a mouse-adapted SARS-CoV-2 strain or WT SARS-CoV-2. Dose levels and immunization schedules predicted to result in optimal and suboptimal protection were included

in these studies in order to identify immune signatures for each regimen. Viral load, viral replication in the upper (nasal turbinates) and lower (lung) airways, and/or lung pathology and inflammation were evaluated after viral challenge.

The potential of mRNA-1273 to promote vaccine-associated ERD was assessed in young and aged mice, hamsters, and NHPs through the evaluation of immunogenicity endpoints (IgG1:IgG2a/c ratio, T-helper 1/T-helper 2 cytokine profiles, and the ratio of binding to neutralizing antibodies) indicative of a protective or disease enhancement phenotype, monitoring of viral load, viral replication, and/or histopathological evaluation of lung tissues after viral challenge.

2.6.1.1.2 Nonclinical Pharmacokinetic Program

Unprotected mRNA is degraded within minutes in biological fluids and is unlikely to persist in tissues; therefore, the biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics, and mRNAs that are within LNPs of the same composition (ie, SM-102-containing LNPs) are expected to distribute similarly to the LNPs. Thus, the non-GLP, single intramuscular (IM) dose, tissue distribution study of mRNA-1647, an mRNA-based cytomegalovirus vaccine that contains 6 mRNA sequences combined in SM-102-containing LNPs, supports the development of mRNA-1273.

2.6.1.1.3 Nonclinical Toxicology Program

The toxicological profile associated with mRNA-based vaccines formulated in SM-102-containing LNPs, including mRNA-1273, is driven primarily by the LNP composition and, to a lesser extent, the biologic activity of the expressed antigens of the vaccine. The aggregate toxicology profile observed across 6 GLP rat repeat-dose toxicology studies for 5 different SM-102-containing LNP vaccines, together with a non-GLP repeat-dose immunogenicity rat study with safety endpoints and genotoxicity assessments of the SM-102 lipid, supports the development of mRNA-1273. The safety and tolerability of mRNA-based vaccines that encode for various antigens and are formulated in SM-102-containing LNPs (mRNA-1706, mRNA-1653, mRNA-1893, mRNA-1647, and mRNA-1443) have been evaluated in multiple GLP-compliant repeat-dose toxicity studies in Sprague Dawley rats. Additionally, the Sponsor completed a repeat-dose non-GLP study in Sprague Dawley rats to characterize the immunogenic response and potential toxicity of mRNA-1273 at clinically relevant doses. SM-102, the novel lipid used in mRNA-1273, was evaluated in genotoxicity studies as an individual agent using a standard ICH S2 (R1) approach ([ICH 2011](#)), including a GLP-compliant

bacterial reverse mutation (Ames) test and a GLP-compliant in vitro micronucleus test in human peripheral blood lymphocytes. In addition, SM-102 was evaluated for in vivo genotoxicity risk in a GLP-compliant in vivo rat micronucleus test using an mRNA-based vaccine formulated in SM-102 LNPs (mRNA-1706) and in a non-GLP-compliant in vivo rat micronucleus test using a reporter mRNA (nascent peptide imaging luciferase mRNA) CCI [REDACTED]

Overall, the data from the nonclinical testing program presented in this submission demonstrate that mRNA-1273 is safe and well tolerated, is immunogenic, fully protects animals from viral challenge at optimal dose levels, and does not promote ERD at either protective or subprotective dose levels. These data support the clinical evaluation of the efficacy and safety of 100 µg of mRNA-1273 administered as 2 IM injections 28 days apart.

2.6.2 REFERENCES

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